*REMARKS/ARGUMENTS*

*The Pending Claims*

Claims 1, 3, 4, and 13 are currently pending and are directed to a method for the therapeutic treatment of a carcinoma in a mammal.

*Amendments to the Specification*

The specification has been amended to include a replacement sequence listing comprising SEQ ID NO: 9 and include an incorporation-by-reference of electronically filed material (i.e., the replacement sequence listing).

The amino acid sequence of SEQ ID NO: 9, which is the FGFR-4 sequence of EMBL Gene Bank accession number X57205, was incorporated by reference to the Gene Bank accession number at page 9, lines 17-20, of the specification.

Accordingly, no new matter has been added by way of these amendments to the specification.

*The Amendments to the Claims*

The claims have been amended to point out more particularly and claim more distinctly the present invention. Claim 1 has been amended to incorporate the subject matter of claims 7, 11, and 12. As a result, claims 7, 11, and 12 have been canceled.

Claim 1 also has been amended to refer to SEQ ID NO: 9, which is the FGFR-4 sequence of EMBL Gene Bank accession number X57205 (see, for example, page 9, lines 17-20, of the specification), which has been added to the sequence listing.

Claims 1 and 3 have been amended to recite "carcinoma" as supported by the specification at, for example, page 11, line 33, through page 12, line 3.

Claim 13 has been amended to clarify the claim language in view of the amendment to claim 1.

No new matter has been added by way of these amendments to the claims.

*The Office Action*

The Office rejects claims 1, 3, 4, 7, and 11-13 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office rejects claims 1, 3, 4, 7, and 11-13 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Reconsideration of these rejections is hereby requested.

*Discussion of Rejection Under 35 U.S.C. § 112, Second Paragraph*

The Office alleges that there is no nexus in claim 1 between the cancer and the mutated FGFR-4 protein.

Altered activity of FGFR-4 (e.g., as a result of mutated FGFR-4) leads to increased division activity and a degenerated cancer cell (see page 7, lines 17-26, of the specification). In particular, a point mutation at position 388 of SEQ ID NO: 9, in which glycine is substituted with arginine, results in receptor tyrosine kinases becoming active in an altered way, which results in signal transfer without ligand stimulation (see page 10, lines 27-32, of the specification). As a result, an uncontrollable growth of cells is triggered, which leads to cancer (see page 10, lines 27-32, of the specification).

As set forth in the specification, cell lines derived from breast tumors, squamous cell carcinoma, glioblastomas, neuroblastomas, and uterine cancer, which are all carcinomas, carried the point mutation at position 388 (see page 11, lines 17-33). Inhibitors of the mutated FGFR-4, such as kinase-inactive receptors, are suitable for the treatment of carcinomas (see page 11, line 33, through page 12, line 6, of the specification), as recited in the pending claims.

The Office also alleges that it is unclear whether the mammal of claim 1 is a transgenic animal engineered to express the mutated FGFR-4 protein or whether the mammal has an endogenous mutated FGFR-4 protein.

The pending claims are directed to the therapeutic treatment of carcinoma in a mammal comprising a mutated FGFR-4 protein. The claims encompass mammals with a mutated FGFR-4 protein, regardless of how the mammal acquired the mutation. As described above, the presence of the mutated FGFR-4 protein leads to carcinomas.

Therefore, the administration of an inhibitor of the FGRF-4 protein results in the treatment of a carcinoma.

It is apparent from the specification , as well as the pending claims, that the invention does not relate to the generation of transgenic animals. The invention is directed to the therapeutic treatment of a carcinoma in a mammal, wherein the mammal comprises a mutated FGFR-4 protein. Based on the specification, it would be apparent to one of ordinary skill in the art that this mutation is not due to genetic engineering, but that it is an allelic variant (see, for example, page 15, lines 15-28; and page 25, lines 15-19, of the specification).

In view of the foregoing, the rejections under Section 112, second paragraph, are moot and should be withdrawn.

*Discussion of Rejection Under 35 U.S.C. § 112, First Paragraph*

The Office alleges that the specification does not enable the treatment of any cancer in a mammal comprising any mutation in the transmembrane domain of a FGFR-4 protein that substitutes a hydrophilic amino acid for a hydrophobic amino acid.

Claim 1, as amended, recites that the mutated FGFR-4 comprises a glycine to arginine substitution at position 388 of SEQ ID NO: 9. As discussed above, this particular mutation is strongly associated with carcinomas (e.g., breast cancer, squamous cell carcinoma, glioblastoma, neuroblastoma, and uterine cancer). Therefore, the administration of inhibitors of the mutated FGFR-4, such as kinase-inactive receptors, result in the therapeutic treatment of a carcinoma, as set forth in the pending claims.

The Office cites to Streit et al. (*Br. J. Cancer, 94*: 1879-1886 (2006)) and Mawrin et al. (*Cancer Letters, 239*: 239-245 (2006)) as support for the Office's contention that the specification does not enable the treatment of any cancer in the mammal. Steit et al. teaches that, despite the fact that the Arg388 allele correlates with tumor thickness, there is apparently no correlation of the FGFR-4 allele and disease-free survival in melanoma patients (see page 1886, right column). Mawrin et al. alleges that the Arg388 allele does not play a major role in glioma (see abstract).

The claims are directed to the therapeutic treatment of a *carcinoma* in a mammal. As set forth in the specification, the use of inhibitors of FGFR-4 Arg388 is especially suitable to the treatment of carcinomas (see page 11, line 33, through page 12, line 1). In addition to the teaching in the specification, several post-filing references correlate the presence of the Arg388 allele of FGFR-4 with a number of proliferative disorders and, in particular, various carcinomas.

Bange et al. (*Cancer Research, 62*: 840-847 (2002)) discloses that the Arg388 allele of FGFR-4 correlates with reduced disease free-survival of breast cancer patients (see abstract; and page 845, paragraph bridging left and right columns) and with early lymph node metastasis and reduced overall survival of patients with colon cancer (see abstract; and page 845, right column, second paragraph).

da Costa Andrade et al. (*Experimental and Molecular Pathology, 82*: 53-57 (2007)) discloses that the Arg388 allele of FGFR-4 is associated with a poor prognosis for positive breast node cancer, high-grade soft tissue sarcoma, colon carcinoma, and head and neck squamous cell carcinoma (see abstract).

Spinola et al. (*Journal of Clinical Oncology, 23:* 7307-7311 (2005)) discloses the role of the Arg388 allele of FGFR-4 in lung adenocarcinoma. Specifically, the Arg388 allele is associated with an earlier cancer onset, a higher proportion of poor clinical stage disease, nodal involvement, and a higher proportion of short-term survivors (see abstract; and page 7311, left column, second paragraph).

Streit et al. (*International Journal of Cancer, 111*: 213-217 (2004)) discloses that a high expression rate of the Arg388 allele of FGFR-4 is significantly associated with reduced overall survival, and with an advanced tumor stage and poor clinical outcome in patients with head and neck squamous cell carcinoma (see abstract; and page 216, right column, last paragraph, through page 217, second paragraph).

Thussbas et al. (*Journal of Clinical Oncology, 24*: 3747-55 (2006)) discloses that the Arg388 allele of FGFR-4 correlates with a poor disease-free survival and overall survival of primary breast cancer node-positive patients. Furthermore, the Arg388 carriers showed a relatively poor therapy response (see abstract; and Figure 2B).

Wang et al. (*Clinical Cancer Research, 10*: 6169-6178 (2004)) discloses that the Arg388 allele of FGFR-4 is strongly associated with the occurrence of prostate cancer and a more aggressive disease progression (see abstract; and paragraph bridging pages 6173-6174).

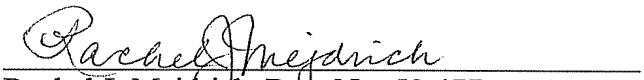
Based on the teachings in the specification and the confirming disclosures of the post-filing references described above, one of ordinary skill in the art would have recognized that the Arg388 allele of FGFR-4 correlates with a large number of carcinomas. The specification discloses that inhibitors of mutated FGFR-4, such as kinase-inactive receptors, are suitable for the treatment of carcinomas. Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success that carcinomas with the FGFR-4 Arg388 protein would respond to a treatment with inhibitors of FGFR-4 Arg388.

In view of the foregoing, the specification provides an enabling disclosure of the pending claims and the enablement rejection should be withdrawn.

*Conclusion*

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



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